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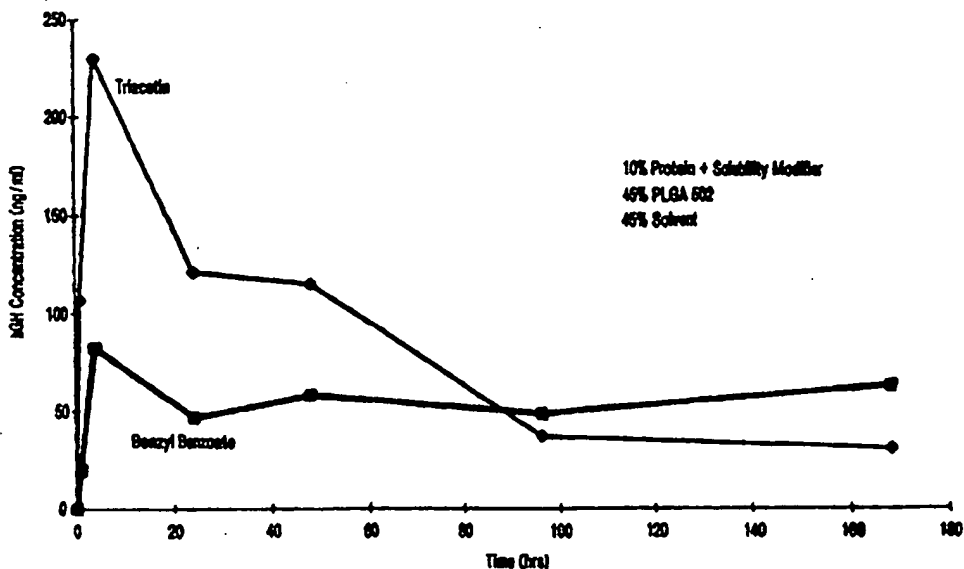
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(21) International Application Number: PCT/US97/23659 (22) International Filing Date: 18 December 1997 (18.12.97) (30) Priority Data: 60/033,439 20 December 1996 (20.12.96) US (71) Applicant (for all designated States except US): ALZA CORPORATION [US/US]; 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): BRODBECK, Kevin, J. [US/US]; 2383 South Court Street, Palo Alto, CA 94301 (US). GAYNOR-DUARTE, Ann, T. [US/US]; 13063 Broadway Terrace, Oakland, CA 94611 (US). SHEN, Theodore, T. [US/US]; 18 Dockside Circle, Redwood City, CA 94065 (US). (74) Agents: DHUEY, John, A. et al.; Alza Corporation, 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published Without international search report and to be republished upon receipt of that report.	

(54) Title: GEL COMPOSITION AND METHODS



(57) Abstract

Methods and compositions for systemically or locally administering by implantation a beneficial agent to a subject are described, and include, for example, compositions having burst indices of 8 or less for systemic applications and systems releasing 10 % or less of the total dose of beneficial agent in the first 24 hours after implantation for local applications. The compositions include a biocompatible polymer, a biocompatible solvent having low water miscibility that forms a viscous gel with the polymer and limits water uptake by the implant, and a beneficial agent.

GEL COMPOSITION AND METHODS

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to a gel composition that can be implanted into a desired location and which can provide controlled release of a beneficial agent. The present invention also relates to methods of controlling release of a beneficial agent from a composition.

Description of the Related Art

Biodegradable polymers have been used for many years in medical applications. Illustrative devices composed of the biodegradable polymers include sutures, surgical clips, staples, implants, and sustained release drug delivery systems. The majority of these biodegradable polymers have been based upon glycolide, lactide, caprolactone, and copolymers thereof.

The biodegradable polymers can be thermoplastic materials which means that they can be heated and formed into various shapes such as fibers, clips, staples, pins, films, etc. Alternatively, they can be thermosetting materials formed by crosslinking reactions which lead to high-molecular-weight materials that do not melt or form flowable liquids at high temperatures.

Although thermoplastic and thermosetting biodegradable polymers have many useful biomedical applications, there are several important limitations to their use in the bodies of various animals including humans, animals, birds, fish, and reptiles. Because these polymers generally are

1 Other illustrative osmotic delivery systems include those disclosed in
2 U.S. Patent Nos. 3,797,492, 3,987,790, 4,008,719, 4,865,845, 5,057,318,
3 5,059,423, 5,112,614, 5,137,727, 5,151,093, 5,234,692, 5,234,693,
4 5,279,608, and 5,336,057. Pulsatile delivery devices are also known which
5 deliver a beneficial agent in a pulsatile manner as disclosed in U.S. Patent
6 Nos. 5,209,746, 5,308,348, and 5,456,679.

7 One way to avoid the incision needed to implant drug delivery systems
8 is to inject them as small particles, microspheres, or microcapsules. For
9 example, U.S. Patent No. 5,019,400 describes the preparation of controlled
10 release microspheres via a very low temperature casting process. These
11 materials may or may not contain a drug which can be released into the body.
12 Although these materials can be injected into the body with a syringe, they do
13 not always satisfy the demand for a biodegradable implant. Because they are
14 particulate in nature, they do not form a continuous film or solid implant with
15 the structural integrity needed for certain prostheses. When inserted into
16 certain body cavities such as a mouth, a periodontal pocket, the eye, or the
17 vagina where there is considerable fluid flow, these small particles,
18 microspheres, or microcapsules are poorly retained because of their small
19 size and discontinuous nature. Further, the particles tend to aggregate and
20 thus their behavior is hard to predict. In addition, microspheres or
21 microcapsules prepared from these polymers and containing drugs for
22 release into the body are sometimes difficult to produce on a large scale, and
23 their storage and injection characteristics present problems. Furthermore,
24 one other major limitation of the microcapsule or small-particle system is their

1 is described as being effective to provide about at least 10% solubility in
2 water. The polymer matrix systems are described as forming a porous core
3 surrounded by a porous skin.

4 U.S. Patent No. 5,242,910 describes a sustained release composition
5 containing drugs for treating periodontal disease. The composition comprises
6 copolymers of lactide and glycolide, triacetin (as a solvent/plasticizer) and an
7 agent providing relief of oral cavity diseases. The composition can take the
8 form of a gel and can be inserted into a periodontal cavity via a syringe using
9 either a needle or a catheter. As additional optional components, the
10 composition can contain surfactants, flavoring agents, viscosity controlling
11 agents, complexing agents, antioxidants, other polymers, gums, waxes/oils,
12 and coloring agents. One illustrative viscosity controlling agent set forth in
13 one of the examples is polyethylene glycol 400.

14 U.S. Patent No. 5,620,700 describes a polymer-drug matrix, optionally
15 including plasticizers in an amount up to about 30 wt %, for local application
16 of drug in the periodontal cavity. Among the plasticizers listed are, *inter alia*,
17 triethyl citrate, acetyl triethyl citrate, tributyl citrate, acetyl tributyl citrate,
18 diethyl phthalate, diethyl tartrate, ethyl lactate, triacetin and diacetin. The
19 polymer matrix is non-flowable prior to administration and is heated to
20 become flowable so that it may be dispensed into the periodontal cavity where
21 it solidifies. While the patent discusses possible systemic applications by
22 delivery via the ocular sacs of the eye or intravaginal delivery, it does not
23 address the issue of burst of drug or methods of controlling burst.

1 agent can result in adverse consequences to the subject being treated, or
2 where it is necessary to mimic the naturally-occurring-daily profile of beneficial
3 agents, such as hormones and the like, in the body of the subject being
4 treated.

5 In an attempt to control burst and modulate and stabilize the delivery of
6 the beneficial agent the prior art has coated particles of beneficial agent to
7 retard release into an aqueous environment and extend release of the
8 beneficial agent over time. Alternatively, various stabilizing or release
9 modulating agents, such as metal salts as described in U.S. Patents
10 5,656,297; 5,654,010; 4,985,404 and 4,853,218 have been used.
11 Notwithstanding some success, those methods have not been entirely
12 satisfactory for the large number of beneficial agents that would be effectively
13 delivered by implants, since in many instances the modulation and
14 stabilization effect is the result of the formation of a complex of the metal ion
15 with the beneficial agent. When such complexes do not form, the
16 stabilization/modulation effect may not be adequate to prevent undesirable
17 "burst" of the beneficial agent upon its introduction into the implant site.

18 Additionally, with conventional low viscosity, solvent-based depot
19 compositions comprised of a polymer dissolved in a solvent, another problem
20 which often exists is that the composition solidifies slowly after injection as
21 solvent diffuses from the depot and water migrates into the depot. Since
22 these compositions are relatively non-viscous in order to be injected, a large
23 percentag of drug may be rapidly released as the system forms by diffusion
24 of the solvent, particularly when the beneficial agent is soluble in the solvent

1 presenting a controlled, sustained release of beneficial agent to the subject
2 being treated. What one observes, then, is a burst of beneficial agent being
3 released in a short time period immediately after implantation, a lag time in
4 which no or very little beneficial agent is being released, and subsequently
5 continued delivery of beneficial agent (assuming beneficial agent remains
6 after the burst) until the supply of beneficial agent is exhausted.

7 SUMMARY OF THE INVENTION

8 The present invention provides a method and an implantable system
9 for systemic and local delivery of a beneficial agent to a subject. The method
10 and system provide controlled release of beneficial agent to the subject being
11 treated and limit the initial burst of beneficial agent from the implant system.
12 Additionally, the invention provides a method of preparing implant systems
13 having restricted initial burst of beneficial agent.

14 In one aspect, the invention comprises a method of administering,
15 locally or systemically, a beneficial agent to a subject which comprises
16 implanting a system comprising a beneficial agent dispersed or dissolved
17 substantially throughout a viscous gel, the system releasing 20% or less by
18 weight of the beneficial agent present in the viscous gel within the first 24
19 hours after implantation in the subject. Preferably, 10% or less by weight of
20 the beneficial agent will be released within the first 24 hours after
21 implantation.

22 In another aspect, the invention comprises a method of systemically
23 administering a beneficial agent to a subject which comprises implanting a

1 having a miscibility in water of less than 7% by weight. Preferably, the
2 miscibility in water of the solvent mixture is 20% or less by weight, and more
3 preferably 10% or less by weight.

4 In yet another aspect, the invention comprises an implantable,
5 biodegradable composition for delivery of a beneficial agent to a subject
6 wherein the composition comprises a polymer; an effective plasticizing
7 amount of a solvent to form a viscous gel with the polymer; and a beneficial
8 agent dissolved or dispersed in the gel, wherein the solvent comprises a
9 single solvent or a mixture of solvents with at least one solvent having a
10 miscibility in water of less than 7% by weight selected from lower alkyl and
11 aralkyl esters of benzoic acid.

12 In another aspect the present invention provides an implantable gel
13 composition for systemic delivery of a beneficial agent to a subject
14 comprising:

15 A) a biocompatible polymer;

16 B) a biocompatible solvent, having miscibility in water of less than
17 7% by weight and capable of dissolving the polymer and forming a viscous
18 gel, said solvent being selected from the group comprising compounds
19 having the following structural formula:



1 In a further aspect, the present invention provides a method of
2 restricting uptake of water by a gel composition which comprises forming the
3 gel composition from a polymer and a solvent that forms a viscous gel with
4 the polymer, the solvent having a miscibility in water of less than 7% by
5 weight. Preferably, the solvent will have a miscibility in water of 6% or less by
6 weight, and more preferably 5% or less by weight.

7 In another aspect, the present invention provides a method of
8 preparing an injectable gel composition comprising:

9 A) mixing a biocompatible polymer and a solvent having a miscibility in
10 water of 7% or less selected from lower alkyl and aralkyl esters of benzoic
11 acid to form a viscous gel;

12 B) dispersing or dissolving a beneficial agent, optionally associated
13 with a solubility modulator of the beneficial agent, in an emulsifying agent to
14 form a beneficial agent containing emulsifying agent; and

15 C) mixing the beneficial agent containing emulsifying agent with the
16 viscous gel, said beneficial agent containing emulsifying agent forming a
17 dispersed droplet phase in the viscous gel, and optionally,

18 D) mixing one or more of a pore former and an osmotic agent with
19 said viscous gel.

20 In another aspect, the present invention provides a method of
21 preparing an implantable gel composition comprising:

22 A) mixing a biocompatible polymer and a solvent having a miscibility in
23 water of 7% or less selected from lower alkyl and aralkyl esters of
24 benzoic acid to form a viscous gel;

- 1 C) a beneficial agent; and optionally, one or more of the following:
- 2 D) an emulsifying agent;
- 3 E) a pore former;
- 4 F) a solubility modulator of the beneficial agent, optionally associated
- 5 with the beneficial agent; and
- 6 G) an osmotic agent;
- 7 wherein at least the beneficial agent, optionally associated with the solubility
- 8 modulator, is maintained separated from the solvent until the time of
- 9 administration of the beneficial agent to a subject.

10 In still another aspect, the invention comprises an implantable

11 composition for the systemic delivery of a beneficial agent comprising a

12 poly(lactide-co-glycolide) copolymer; an effective plasticizing amount of a

13 solvent to form a viscous gel with the polymer; and a beneficial agent

14 selected from the group consisting of cDNA, DNA, peptides, proteins and

15 fragments and derivatives thereof, said composition having a burst index of 8

16 or less.

17 In another aspect, the invention comprises an implantable composition

18 for the sustained delivery of a beneficial agent comprising a poly(lactide-co-

19 glycolide) copolymer; an effective plasticizing amount of a solvent selected

20 from lower alkyl and aralkyl esters of benzoic acid to form a viscous gel with

21 the polymer; and a beneficial agent.

22 In a further aspect, the invention comprises an implantable

23 composition comprising a viscous gel and a beneficial agent dispersed or

1 Figure 3 is a graph illustrating the viscosity profiles of emulsions at
2 different shear rates of water alone and of an aqueous mixture of ethanol,
3 and of the viscous gel without emulsifying agent;

4 Figures 4A and 4B are graphs illustrating the degree of water uptake
5 for various polymer-solvent mixtures, some of which form a part of this
6 invention, and demonstrating that as the miscibility of the solvent in water
7 decreases, the amount of water taken up into the implant decreases; and

8 Figures 5A and 5B are graphs of *in vivo* release rate profiles of non-
9 stabilized and zinc-stabilized human growth hormone from gels formed from
10 PLGA and the solvents triacetin and benzyl benzoate, respectively.

11 DETAILED DESCRIPTION OF THE INVENTION

12 The present invention is directed to a method of systemically or locally
13 administering a beneficial agent to a subject by implanting in the subject an
14 implantable system, formed as a viscous gel from a biocompatible polymer
15 and a biocompatible solvent, and a beneficial agent is substantially dissolved
16 or dispersed throughout the gel. By appropriate choice of solvent, water
17 migration from the aqueous environment surrounding the implant system is
18 restricted, and beneficial agent is released to the subject over a prolonged
19 period of time, thus providing for delivery of the beneficial agent with a
20 controlled burst of beneficial agent and sustained release thereafter.

21 It has been discovered that when a solvent having a solubility in water
22 of less than 7% by weight in water is present in the system, suitable burst
23 control and sustained delivery of beneficial agent is achieved, whether or not
24 a solubility modulator of the beneficial agent is present in the system.

1 pharmaceutical excipients and other additives that do not change the
2 beneficial aspects of the present invention. The addition of a solubility
3 modulator to the implant system may enable the use of a solvent having a
4 solubility of 7% or greater in the implant system with minimal burst and
5 sustained delivery under particular circumstances. However, it is presently
6 preferred that the implant system utilize at least one solvent having a
7 solubility in water of less than 7% by weight, whether the solvent is present
8 alone or as part of a solvent mixture. It has also been discovered that when
9 mixtures of solvents which include a solvent having 7% or less by weight
10 solubility in water and one or more miscible solvents, optionally having
11 greater solubility, are used, implant systems exhibiting limited water uptake
12 and minimal burst and sustained delivery characteristics are obtained.

13 Definitions

14 The term "beneficial agent" means an agent that effects a desired
15 beneficial, often pharmacological, effect upon administration to a human or an
16 animal, whether alone or in combination with other pharmaceutical excipients
17 or inert ingredients.

18 The term "AUC" means the area under the curve obtained from an *in*
19 *vivo* assay in a subject by plotting blood plasma concentration of the
20 beneficial agent in the subject against time, as measured from the time of
21 implantation of the composition, to a time "*t*" after implantation. The time *t* will
22 correspond to the delivery period of beneficial agent to a subject.

23 The term "burst index" means, with respect to a particular composition
24 intended for systemic delivery of a beneficial agent, the quotient formed by

1 that is to be delivered from an implanted composition. It is understood that
2 the initial burst may vary depending on the shape and surface area of the
3 implant. Accordingly, the percentages and burst indices associated with
4 initial burst described herein are intended to apply to compositions tested in a
5 form resulting from dispensing of the composition from a standard syringe.

6 The term "solubility modulator" means, with respect to the beneficial
7 agent, an agent that will alter the solubility of the beneficial agent, with
8 reference to polymer solvent or water, from the solubility of beneficial agent in
9 the absence of the modulator. The modulator may enhance or retard the
10 solubility of the beneficial agent in the solvent or water. However, in the case
11 of beneficial agents that are highly water soluble, the solubility modulator will
12 generally be an agent that will retard the solubility of the beneficial agent in
13 water. The effects of solubility modulators of the beneficial agent may result
14 from intereactions of the solubility modulator with the solvent, or with the
15 beneficial agent itself, such as by the formation of complexes, or with both.
16 For the purposes hereof, when the solubility modulator is "associated" with
17 the beneficial agent, all such interactions or formations as may occur are
18 intended. Solubility modulators may be mixed with the beneficial agent prior
19 to its combination with the viscous gel or may be added to the viscous gel
20 prior to the addition of the beneficial agent, as appropriate.

21 The term "subject" means, with respect to the administration of a
22 composition of the invention, an animal or a human being.

23 Since all solvents, at least on a molecular level, will be soluble in water
24 (i.e., miscible with water) to some very limited extent, the term "immiscible" as

1 polyhydroxycellulose, chitin, chitosan, and copolymers, terpolymers and
2 mixtures thereof.

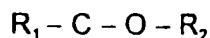
3 Presently preferred polymers are polylactides, that is, a lactic acid-
4 based polymer that can be based solely on lactic acid or can be a copolymer
5 based on lactic acid and glycolic acid which may include small amounts of
6 other comonomers that do not substantially affect the advantageous results
7 which can be achieved in accordance with the present invention. As used
8 herein, the term "lactic acid" includes the isomers L-lactic acid, D-lactic acid,
9 DL-lactic acid and lactide while the term "glycolic acid" includes glycolide.
10 Most preferred are poly(lactide-co-glycolide)copolymers, commonly referred
11 to as PLGA. The polymer may have a monomer ratio of lactic acid/glycolic
12 acid of from about 100:0 to about 15:85, preferably from about 60:40 to about
13 75:25 and an especially useful copolymer has a monomer ratio of lactic
14 acid/glycolic acid of about 50:50.

15 The lactic acid-based polymer has a number average molecular weight
16 of from about 1,000 to about 120,000, preferably from about 5,000 to about
17 30,000 as determined by gas phase chromatography. As indicated in
18 aforementioned U.S. Patent No. 5,242,910, the polymer can be prepared in
19 accordance with the teachings of U.S. Patent No. 4,443,340. Alternatively,
20 the lactic acid-based polymer can be prepared directly from lactic acid or a
21 mixture of lactic acid and glycolic acid (with or without a further comonomer)
22 in accordance with the techniques set forth in U.S. Patent No. 5,310,865.
23 The contents of all of these patents are incorporated by reference. Suitable
24 lactic acid-based polymers are available commercially. For instance, 50:50

1 20°C, and weighed, and a candidate solvent is added dropwise. The solution
2 is swirled to observe phase separation. When the saturation point appears to
3 be reached, as determined by observation of phase separation, the solution
4 is allowed to stand overnight and is re-checked the following day. If the
5 solution is still saturated, as determined by observation of phase separation,
6 then the percent (w/w) of solvent added is determined. Otherwise more
7 solvent is added and the process repeated. Solubility or miscibility is
8 determined by dividing the total weight of solvent added by the final weight of
9 the solvent/water mixture. When solvent mixtures are used, for example 20%
10 triacetin and 80% benzyl benzoate, they are pre-mixed prior to adding to the
11 water.

12 Solvents useful in this invention are generally less than 7% water
13 soluble by weight as described above. Solvents having the above solubility
14 parameter may be selected from the lower alkyl and aralkyl esters of aryl
15 acids such as benzoic acid, the phthalic acids, salicylic acid, lower alkyl
16 esters of citric acid, such as triethyl citrate and tributyl citrate and the like, and
17 aryl, aralkyl and lower alkyl ketones. Among preferred solvents are those
18 having solubilities within the foregoing range selected from (i) compounds
19 having the following structural formulas :

20 O



1 polypropylene glycol dibenzoate, propylene glycol dibenzoate, diethylene
2 glycol benzoate and dipropylene glycol benzoate blend, polyethylene glycol
3 (200) dibenzoate, iso decyl benzoate, neopentyl glycol dibenzoate, glyceryl
4 tribenzoate, pentaerythritol tetrabenzoate, cumylphenyl benzoate, trimethyl
5 pentanediol dibenzoate.

6 Art recognized phthalic acid derivatives from which solvents having the
7 requisite solubility may be selected include: Alkyl benzyl phthalate, bis-
8 cumyl-phenyl isophthalate, dibutoxyethyl phthalate, dimethyl phthalate,
9 dimethyl phthalate, diethyl phthalate, dibutyl phthalate, diisobutyl phthalate,
10 butyl octyl phthalate, diisooheptyl phthalate, butyl octyl phthalate, diisonoyl
11 phthalate, nonyl undecyl phthalate, dioctyl phthalate, di-iso octyl phthalate,
12 dicapryl phthalate, mixed alcohol phthalate, di-(2-ethylhexyl) phthalate, linear
13 heptyl, nonyl, phthalate, linear heptyl, nonyl, undecyl phthalate, linear nonyl
14 phthalate, linear nonyl undecyl phthalate, linear dinoyl, didecyl phthalate
15 (diisodecyl phthalate), diundecyl phthalate, ditridecyl phthalate,
16 undecyldodecyl phthalate, decyltridecyl phthalate, blend (50/50) of dioctyl and
17 didecyl phthalates, butyl benzyl phthalate, and dicyclohexyl phthalate.

18 Preferred solvents include the lower alkyl and aralkyl esters of the aryl
19 acids described above. Representative acids are benzoic acid and the
20 phthalic acids, such as phthalic acid, isophthalic acid, and terephthalic acid.
21 Most preferred solvents are derivatives of benzoic acid and include, but are
22 not limited to, methyl benzoate, ethyl benzoate, n-propyl benzoate, isopropyl
23 benzoate, butyl benzoate, isobutyl benzoate, sec-butyl benzoate, *tert*-butyl

1 Component solvents useful in component solvent mixtures are those
2 solvents that are miscible with the primary solvent or solvent mixture, and
3 include, but are not limited, to triacetin, diacetin, tributyrin, triethyl citrate,
4 tributyl citrate, acetyl triethyl citrate, acetyl tributyl citrate, triethylglycerides,
5 triethyl phosphate, diethyl phthalate, diethyl tartrate, mineral oil, polybutene,
6 silicone fluid, glycerin, ethylene glycol, polyethylene glycol, octanol, ethyl
7 lactate, propylene glycol, propylene carbonate, ethylene carbonate,
8 butyrolactone, ethylene oxide, propylene oxide, N-methyl-2-pyrrolidone, 2-
9 pyrrolidone, glycerol formal, methyl acetate, ethyl acetate, methyl ethyl
10 ketone, dimethylformamide, dimethyl sulfoxide, tetrahydrofuran, caprolactam,
11 decylmethylsulfoxide, oleic acid, and 1-dodecylazacyclo-heptan-2-one, and
12 mixtures thereof.

13 In an especially preferred embodiment, the primary solvent is selected
14 from lower alkyl and aralkyl esters of benzoic acid and the polymer is a lactic-
15 acid based polymer, most preferably PLGA, having a number average
16 molecular weight of between about 8,000 to about 13,000, preferably about
17 10,000. Presently, the most preferred solvents are benzyl benzoate and the
18 lower alkyl esters of benzoic acid. The benzoic acid esters may be used
19 alone or in a mixture with other miscible solvents, e.g., triacetin, as described
20 herein. Implants are prepared as viscous gels in which the beneficial agent is
21 dissolved or dispersed substantially throughout, and such compositions are
22 useful both for systemic and local administration of beneficial agent, whether
23 or not initial burst is an important consideration. Additionally, use of esters of
24 benzoic acid provides increased control of water migration resulting in

1 shown in Figure 4A, water uptake by a gel vehicle formed with the more water
2 miscible solvent N-methyl-2-pyrrolidone (NMP) is higher than that for any
3 other solvent-polymer combination, by about a factor of four or more. Water
4 uptake for the combination of 80% benzyl benzoate and 20% NMP by weight
5 in the solvent portion of the vehicle is less than a third that of NMP alone.
6 Implants with benzyl benzoate take up the least water, whether compared to
7 the other solvents alone or as mixtures with benzyl benzoate. Additionally, it
8 can be seen that the 80/20 mixture of benzyl benzoate and triacetin takes up
9 less than 10% water on a weight basis, and exhibits less water uptake than
10 triacetin alone. Figure 4B provides a comparison of various solvents alone
11 and demonstrates again the advantages of the benzoic acid esters,
12 particularly that of benzyl benzoate. A relative comparison of the water
13 uptake for the various solvents and the burst indices reproduced in the
14 foregoing Table 1 show a correlation between low water uptake values and
15 low burst indices. Gel compositions of this invention may take up 25 % or
16 less of their bulk weight in water within the first 7 days, 30% in the first 14
17 days and 40% in the first 21 days, as tested in the water migration assay
18 described herein.

19

20

1 hours after implantation may be reduced by one-third to two-thirds or more by the use of
2 solubility modulators associated with the beneficial agent. Such modulators are typically
3 coatings, substances that form complexes or otherwise associate with or stabilize the
4 beneficial agent such as metallic ions, other stabilizing agents, waxes, lipids, oils, non-
5 polar emulsions, and the like. Use of such solubility modulators may permit the use of
6 more highly water soluble solvents or mixtures and achieve burst indices of 8 or less for
7 systemic applications, or with respect to local applications, release of beneficial agent in
8 the first 24 hours after implantation of not greater than 20% of the beneficial agent
9 administered. Preferably that release will be not greater than 15% and more preferably
10 not greater than 10%.

11 Limited water uptake by the compositions of this invention can often provide the
12 opportunity to prepare compositions without solubility modulators when in other
13 compositions such modulators would be necessary. For example with reference to
14 Table 1, suitable burst indices are obtained for a composition of PLGA, benzyl benzoate
15 and human growth hormone without the presence of Zn ion. Similar results may be
16 obtained with other beneficial agents, such as the interferons, including interferon alpha-
17 2a, interferon alpha-2b and consensus interferon.

18 In instances where the choice of solvent and polymer result in compositions
19 severely restricting water uptake by themselves, it may be desirable to add osmotic
20 agents or other agents and hydroattractants that facilitate water uptake to desired levels.
21 Such agents may be, for example, sugars and the like, and are well known in the art.

1 beneficial agent, potential adverse consequences due to overdosing, cost of
2 beneficial agent, and the type of effect desired, e.g., systemic or local.
3 Preferably, 20% or less of the beneficial agent will be released in the first 24
4 hours after implantation, where the percentage is based on the total amount
5 of beneficial agent to be delivered over the duration of the delivery period.
6 Typically, higher percentages of release in the first 24 hours can be tolerated
7 if the duration of the delivery period is relatively short, e.g., less than 7-14
8 days, or if the beneficial agent has a wide therapeutic window with little
9 likelihood of side effects, or if the beneficial agent acts locally.

10 Depending on the particular solvent or solvent mixture selected, the
11 polymer and beneficial agent, and optionally solubility modulators of the
12 beneficial agent, the compositions of the present invention intended for
13 systemic delivery may provide a gel composition having a burst index of 8 or
14 less, preferably 6 or less, more preferably 4 or less and most preferably 2 or
15 less. Compositions of PLGA with solvents having a miscibility in water of less
16 than 7% by weight, optionally combined with the other solvents, providing
17 implants intended for systemic delivery of beneficial agent having a burst
18 index of 10 or less, preferably 7 or less, more preferably 5 or less and most
19 preferably 3 or less, are particularly advantageous. The use of solvent
20 mixtures as discussed herein can be particularly advantageous as a means of
21 providing sufficient plasticizing of the polymer to obtain viscous gel formation
22 and at the same time meet the desired burst indices and percentage release
23 objectives of the compositions of the invention.

1 The solvent or solvent mixture is typically present in an amount of from
2 about 95 to about 20% by weight and is preferably present in an amount of
3 from about 70 to about 30% by weight and often 60-40% by weight of the
4 viscous gel, i.e., the combined amounts of the polymer and the solvent. The
5 viscous gel formed by mixing the polymer and the solvent typically exhibits a
6 viscosity of from about 1,000 to about 200,000 poise, preferably from about
7 5,000 to about 50,000 poise measured at a 1.0 sec^{-1} shear rate and 25°C
8 using a Haake Rheometer at about 1-2 days after mixing is completed.
9 Mixing the polymer with the solvent can be achieved with conventional low
10 shear equipment such as a Ross double planetary mixer for from about 10
11 minutes to about 1 hour, although shorter and longer periods may be chosen
12 by one skilled in the art depending on the particular physical characteristics of
13 the composition being prepared. Since it is often desirable to administer the
14 implant as an injectable composition, a countervailing consideration when
15 forming implants that are viscous gels is that the polymer/solvent/beneficial
16 agent composition have sufficiently low viscosity in order to permit it to be
17 forced through a small diameter, e.g., 18-20 gauge needle. If necessary,
18 adjustment of viscosity of the gel for injection can be accomplished with
19 emulsifying agents as described herein. Yet, such compositions should have
20 adequate dimensional stability so as to remain localized and be able to be
21 removed if necessary. The particular gel or gel-like compositions of the
22 present invention satisfy such requirements.

23 If the polymer composition is to be administered as an injectable gel,
24 the level of polymer dissolution will need to be balanced with the resulting gel

1 an average diameter of less than about 100 microns. The continuous phase
2 is formed of the polymer and the solvent. The particles of the beneficial agent
3 may be dissolved or dispersed in either the continuous phase or the droplet
4 phase. In the resulting thixotropic composition, the droplets of emulsifying
5 agent elongate in the direction of shear and substantially decrease the
6 viscosity of the viscous gel formed from the polymer and the solvent. For
7 instance, with a viscous gel having a viscosity of from about 5,000 to about
8 50,000 poise measured at 1.0 sec^{-1} at 25°C , one can obtain a reduction in
9 viscosity to less than 100 poise when emulsified with a 10% ethanol/water
10 solution at 25°C as determined by Haake Rheometer.

11 When used, the emulsifying agent typically is present in an amount
12 ranging from about 5 to about 80%, preferably from about 20 to about 60%
13 and often 30 to 50% by weight based on the amount of the injectable depot
14 gel composition, that is the combined amounts of polymer, solvent,
15 emulsifying agent and beneficial agent. Emulsifying agents include, for
16 example, solvents that are not fully miscible with the polymer solvent or
17 solvent mixture. Illustrative emulsifying agents are water, alcohols, polyols,
18 esters, carboxylic acids, ketones, aldehydes and mixtures thereof. Preferred
19 emulsifying agents are alcohols, propylene glycol, ethylene glycol, glycerol,
20 water, and solutions and mixtures thereof. Especially preferred are water,
21 ethanol, and isopropyl alcohol and solutions and mixtures thereof. The type
22 of emulsifying agent affects the size of the dispersed droplets. For instance,
23 ethanol will provide droplets that have average diameters that can be on the

1 tissue or bone. Such applications may permit loading of beneficial agent in
2 the gel above concentrations typically present with injectable compositions.

3 The beneficial agent can be any physiologically or pharmacologically
4 active substance or substances optionally in combination with
5 pharmaceutically acceptable carriers and additional ingredients such as
6 antioxidants, stabilizing agents, permeation enhancers, etc. that do not
7 substantially adversely affect the advantageous results that can be attained
8 by the present invention. The beneficial agent may be any of the agents
9 which are known to be delivered to the body of a human or an animal and
10 that are preferentially soluble in water rather than in the polymer-dissolving
11 solvent. These agents include drug agents, medicaments, vitamins,
12 nutrients, or the like. Included among the types of agents which meet this
13 description are lower molecular weight compounds, proteins, peptides,
14 genetic material, nutrients, vitamins, food supplements, sex sterilants, fertility
15 inhibitors and fertility promoters.

16 Drug agents which may be delivered by the present invention include
17 drugs which act on the peripheral nerves, adrenergic receptors, cholinergic
18 receptors, the skeletal muscles, the cardiovascular system, smooth muscles,
19 the blood circulatory system, synaptic sites, neuroeffector junctional sites,
20 endocrine and hormone systems, the immunological system, the reproductive
21 system, the skeletal system, autacoid systems, the alimentary and excretory
22 systems, the histamine system and the central nervous system. Suitable
23 agents may be selected from, for example, proteins, enzymes, hormones,
24 polynucleotides, nucleoproteins, polysaccharides, glycoproteins, lipoproteins,

1 indoprofen, nitroglycerin, isosorbide dinitrate, propranolol, timolol, atenolol,
2 alprenolol, cimetidine, clonidine, imipramine, levodopa, chlorpromazine,
3 methyldopa, dihydroxyphenylalanine, theophylline, calcium gluconate,
4 ketoprofen, ibuprofen, cephalexin, erythromycin, haloperidol, zomepirac,
5 ferrous lactate, vincamine, diazepam, phenoxybenzamine, diltiazem,
6 milrinone, mandol, quanbenz, hydrochlorothiazide, ranitidine, flurbiprofen,
7 fenufen, fluprofen, tolmetin, alclofenac, mefenamic, flufenamic, difuinal,
8 nimodipine, nitrendipine, nisoldipine, nicardipine, felodipine, lidoflazine,
9 tiapamil, gallopamil, amlodipine, mioflazine, lisinopril, enalapril, enalaprilat,
10 captopril, ramipril, famotidine, nizatidine, sucralfate, etintidine, tetratolol,
11 minoxidil, chlordiazepoxide, diazepam, amitriptyline, and imipramine. Further
12 examples are proteins and peptides which include, but are not limited to,
13 bone morphogenic proteins, insulin, colchicine, glucagon, thyroid stimulating
14 hormone, parathyroid and pituitary hormones, calcitonin, renin, prolactin,
15 corticotrophin, thyrotropic hormone, follicle stimulating hormone, chorionic
16 gonadotropin, gonadotropin releasing hormone, bovine somatotropin, porcine
17 somatotropin, oxytocin, vasopressin, GRF, somatostatin, lypressin,
18 pancreozymin, luteinizing hormone, LHRH, LHRH agonists and antagonists,
19 leuprolide, interferons such as interferon alpha-2a, interferon alpha-2b, and
20 consensus interferon, interleukins, growth hormones such as human growth
21 hormone and its derivatives such as methione-human growth hormone and
22 des-phenylalanine human growth hormone, bovine growth hormone and
23 porcine growth hormone, fertility inhibitors such as the prostaglandins, fertility
24 promoters, growth factors such as insulin-like growth factor, coagulation

1 those compounds that are clinically useful and effective but may have
2 adverse side effects.

3 To the extent not mentioned above, the beneficial agents described in
4 aforementioned U.S. Patent No. 5,242,910 can also be used. One particular
5 advantage of the present invention is that materials, such as proteins, as
6 exemplified by the enzyme lysozyme, and cDNA, and DNA incorporated into
7 vectors both viral and nonviral, which are difficult to microencapsulate or
8 process into microspheres can be incorporated into the compositions of the
9 present invention without the level of degradation caused by exposure to high
10 temperatures and denaturing solvents often present in other processing
11 techniques.

12 The beneficial agent is preferably incorporated into the viscous gel
13 formed from the polymer and the solvent in the form of particles typically
14 having an average particle size of from about 0.1 to about 100 microns,
15 preferably from about 1 to about 25 microns and often from 2 to 10 microns.
16 For instance, particles having an average particle size of about 5 microns
17 have been produced by spray drying or freeze drying an aqueous mixture
18 containing 50% sucrose and 50% chicken lysozyme (on a dry weight basis)
19 and mixtures of 10-20% hGH and 15-30 mM zinc acetate. Such particles
20 have been used in certain of the examples illustrated in the figures.
21 Conventional lyophilization processes can also be utilized to form particles of
22 beneficial agents of varying sizes using appropriate freezing and drying
23 cycles.

1 Release rates and loading of beneficial agent will be adjusted to
2 provide for therapeutically-effective delivery of the beneficial agent over the
3 intended sustained delivery period. Preferably, the beneficial agent will be
4 present in the polymer gel at concentrations that are above the saturation
5 concentration of beneficial agent in water to provide a drug reservoir from
6 which the beneficial agent is dispensed. While the release rate of beneficial
7 agent depends on the particular circumstances, such as the beneficial agent
8 to be administered, release rates on the order of from about 0.1 to about 100
9 micrograms/day, preferably from about 1 to about 10 micrograms per day, for
10 periods of from about 7 to about 90 days can be obtained. Greater amounts
11 may be delivered if delivery is to occur over shorter periods. Generally,
12 higher release rate is possible if a greater burst can be tolerated. In
13 instances where the gel composition is surgically implanted, or used as a
14 "leave behind" depot when surgery to treat the disease state or another
15 condition is concurrently conducted, it is possible to provide higher doses that
16 would normally be administered if the implant was injected. Further, the dose
17 of beneficial agent may be controlled by adjusting the volume of the gel
18 implanted or the injectable gel injected. As can be seen from Figure 2 with
19 respect to lysozyme, with more highly viscous systems, one can avoid a burst
20 effect and deliver on the order of 1% by weight of the beneficial agent in the
21 composition during the first day.

22 Figures 5A and 5B illustrate representative release profiles of human
23 growth hormone ("hGH") obtained in rats from preferred compositions of this
24 invention. The benefits of benzyl benzoate are apparent in that comparison.

1 modulator or stabilizing agent to beneficial agent of about 100:1 to 1:1,
2 preferably 10:1 to 1:1, typically can be utilized.

3 Pore forming agents include, biocompatible materials that when
4 contacted with body fluids dissolve, disperse or degrade to create pores or
5 channels in the polymer matrix. Typically, organic and non-organic materials
6 that are water soluble such as sugars (e.g., sucrose, dextrose), water soluble
7 salts (e.g., sodium chloride, sodium phosphate, potassium chloride, and
8 sodium carbonate), water soluble solvents such as N-methyl-2-pyrrolidone
9 and polyethylene glycol and water soluble polymers (e.g.,
10 carboxmethylcellulose, hydroxypropylcellulose, and the like) can conveniently
11 be used as pore formers. Such materials may be present in amounts varying
12 from about 0.1% to about 100% of the weight of the polymer, but will typically
13 be less than 50% and more typically less than 10-20% of the weight of
14 polymer.

15 Compositions of this invention without beneficial agent are useful for
16 wound healing, bone repair and other structural support purposes.

17 To further understand the various aspects of the present invention, the
18 results set forth in the previously described Figures were obtained in
19 accordance with the following examples.

20 Example 1

21 Lysozyme particles were made by spray drying 50% sucrose and 50%
22 chicken lysozyme (on a dry weight basis).

23 A viscous gel material was prepared by heating 60% by weight of
24 triacetin with 40% by weight of a 50:50 lactic acid:glycolic acid copolymer to

1 hGH solution (5 mg/ml) solution in water (BresaGen Corporation,
2 Adelaide, Australia) was concentrated to 10 mg/mL using a Concentration/
3 Dialysis Selector diafiltering apparatus. The diafiltered hGH solution was
4 then washed with 5 times volume of tris or phosphate buffer solution (pH 7.6).
5 Particles of hGH were then formed by spray drying or lyophilization using
6 conventional techniques. Phosphate buffer solutions (5 or 50 mM) containing
7 hGH (5 mg/mL) and various levels of zinc acetate (0 to 30 mM) were spray-
8 dried using a Yamato Mini Spraydryer set at the following parameters:

Spray Dryer Parameter	Setting
Atomizing Air	2 psi
Inlet Temperature	120°C
Aspirator Dial	7.5
Solution Pump	2-4
Main Air Valve	40-45 psi

9
10 hGH particles having a size range between 2 - 100 microns were obtained.
11 Lyophilized particles were prepared from tris buffer solutions (5 or 50 mM: pH
12 7.6) containing hGH (5 mg/mL) and various levels of zinc acetate (0 to 30
13 mM) using a Durastop μ P Lyophilizer in accordance with the following
14 freezing and drying cycles:

Freezing Cycle	Ramp down at 2.5 C/min to -30 C and hold for 30 minutes
	Ramp down at 2.5 C/min from -30 C to -50C and hold for 60 minutes
Drying Cycle	Ramp up at 0.5 C/min to 10 C and hold for 960 min
	Ramp up at 0.5 C/min to 20 C and hold for 480 min
	Ramp up at 0.5 C/min to 25 C and hold for 300 min
	Ramp up at 0.5 C/min to 30 C and hold for 300 min
	Ramp down at 0.5 C/min to 5 C and hold for 5000 min

15
16
17 hGH particles having a size range between 2 - 100 microns were obtained.

1 spatula, resulting in a sticky amber paste-like substance containing white
2 polymer particles. The vessel containing the polymer/solvent mixture was
3 sealed and placed in a temperature controlled incubator equilibrated to 39°C.
4 The polymer/solvent mixture was removed from the incubator when it appeared
5 to be a clear amber homogeneous gel. Incubation time intervals ranged from 1
6 to 4 days, depending on solvent and polymer type and solvent and polymer
7 ratios. Additional depot gel vehicles are prepared with the following polymers:
8 Poly (D,L-lactide-co-glycolide) 50:50 RESOMER® L104, PLGA-L104, code no.
9 33007, Poly (D,L-lactide-co-glycolide) 50:50 RESOMER® RG206, PLGA-206,
10 code no. 8815, Poly (D,L-lactide-co-glycolide) 50:50 RESOMER® RG502,
11 PLGA-502, code 0000366, Poly (D,L-lactide-co-glycolide) 50:50 RESOMER®
12 RG502H, PLGA-502H, code no. 260187, Poly (D,L-lactide-co-glycolide) 50:50
13 RESOMER® RG503, PLGA-503, code no. 0080765, Poly (D,L-lactide-co-
14 glycolide) 50:50 RESOMER® RG506, PLGA-506, code no. 95051, Poly (D,L-
15 lactide-co-glycolide) 50:50 RESOMER® RG755, PLGA-755, code no. 95037,
16 (Boehringer Ingelheim Chemicals, Inc., Petersburg, VA), and the following
17 solvents or mixtures: glyceryl triacetate (Eastman Chemical Co., Kingsport,
18 TN), benzyl benzoate ("BB"), ethyl benzoate ("EB"), methyl benzoate ("MB"),
19 triacetin ("TA"), and triethyl citrate ("TC") (Aldrich Chemical Co., St Louis, MO).
20 When solvent combinations were used, for example 20% triacetin and 80%
21 benzyl benzoate, the solvent mixture was directly added to the pre-weighed dry
22 polymer. Typical polymer molecular weights were in the range of 14,400 -
23 39,700 (M_w) [6,400-12,200 (M_n)]. Representative gel vehicles are described in
24 Table 2 below.

Table 3: In Vivo hGH

Formulation	Polymer		Solvent		Drug Particle			Trizma Buffer (mM)
	Level	PLGA	Level	Type	Level	Process	Zinc Level (mM)	
A	45%	502	45%	TA	10%	L	0	50
B	45%	502	45%	TA	10%	L	7.5	50
C	45%	502	45%	TA	10%	L	15	50
D	45%	502	45%	BB	10%	L	0	50
E	45%	502	45%	BB	10%	L	7.5	50
F	45%	502	45%	BB	10%	L	15	50
G	45%	502	45%	NMP	10%	L	0	50
H	45%	502	45%	NMP	10%	L	15	50
I	45%	502	45%	TA	10%	SD	0	50
J	45%	502	45%	TA	10%	SD	7.5	50
K	45%	502	45%	BB	10%	SD	0	50
L	45%	502	45%	BB	10%	SD	7.5	50

Table 4: In Vivo hGH (zinc level in all cases was 15 mM)

Formulation	Polymer		Solvent		Drug Particle		Trizma Buffer (mM)
	Level	PLGA	Level	Type	Level	Process	
F	45%	502	45%	BB	10%	L	50
N	45%	502	45%	80%BB/20%TA	10%	L	5
P	45%	502H	45%	TA	10%	L	5
Q	45%	502H	45%	BB	10%	L	5
R	45%	502	45%	EB	10%	L	5
S	45%	502	45%	TC	10%	L	5
T	40%	502	40%	BB	20%	L	5
W	45%	502-2	45%	BB	10%	L	5
X	45%	502	45%	TA	10%	L	5

Example 3 - Lysozyme In Vitro Studies

Lysozyme from chicken egg white (Sigma Chemical Co., St Louis, MO)

in vitro release studies were used to test different vehicle formulations with the highly water soluble solvent NMP and the less soluble solvents triacetin and benzyl benzoate useful in the present invention. A depot gel formulation was dispensed from a 3 cc disposable syringe and weighed onto a Delrin™ cup platform or a 250 μ mesh 1 square inch polypropylene screen. Then, the cup or screen containing a depot gel formulation was immersed into a plastic

1 and final depot gel vehicle weights were recorded to observe weight change.
2 Water content was obtained from depot gel vehicles using a Karl Fischer
3 Apparatus, Mitsubishi Moisture Meter CA-06 equipped with Vaporizer VA-06.
4 Results are illustrated in Figures 4A-4B for selected gels. Those results
5 demonstrate that gel compositions of this invention take up substantially less
6 water than gel compositions formed with NMP alone.

7 Example 5 - hGH In Vivo Studies

8 In vivo studies in rats were performed following an open protocol to determine
9 serum levels of hGH upon systemic administration of hGH via the implant
10 systems of this invention. Depot gel hGH formulations, spray-dried (SD) or
11 lyophilized (L), were loaded into customized 0.5 cc disposable syringes.
12 Disposable 16 gauge needles were attached to the syringes and were heated
13 to 37°C using a circulator bath. Depot gel hGH formulations were injected
14 into rats and blood was drawn at specified time intervals. All serum samples
15 were stored at 4°C prior to analysis. Samples were analyzed for intact hGH
16 content using a radio immuno assay (RIA). Representative results for
17 triacetin and benzyl benzoate are illustrated in Figures 5A and 5B, and
18 demonstrate the superior control of burst by the compositions of the present
19 invention.

20 Example 6

21 Implant systems of this invention are prepared in accordance with
22 Example 2 with equivalent quantities of interferon alpha-2a and -2b,
23 consensus interferon, methionine human growth hormone, des-phenylalanine
24 human growth hormone, carboplatin and insulin-like growth factor. The

1 burst effect and provide the desired beneficial agent release profile.
2 Furthermore, once the beneficial agent has been fully administered, there is
3 no need to remove the composition since it is fully biodegradable. As a still
4 further advantage, the present invention avoids the use of microparticle or
5 microencapsulation techniques which can degrade certain beneficial agents,
6 like peptide and nucleic acid-based drugs and which microparticles and
7 microcapsules may be difficult to remove from the environment of use. Since
8 the viscous gel is formed without the need for water, temperature extremes,
9 or other solvents, suspended particles of beneficial agent remain dry and in
10 their original configuration, which contributes to the stability of thereof.
11 Further, since a mass is formed, the injectable depot gel composition may be
12 retrieved from the environment of use if desired.

13 The above-described exemplary embodiments are intended to be
14 illustrative in all respects, rather than restrictive, of the present invention.
15 Thus the present invention is capable of many variations in detailed
16 implementation that can be derived from the description contained herein by
17 a person skilled in the art. All such variations and modifications are
18 considered to be within the scope and spirit of the present invention as
19 defined by the following claims.

1 7. The method of Claim 5 wherein the polymer is a lactic acid-based
2 polymer and the solvent is selected from lower alkyl and aralkyl esters of
3 benzoic acid.

4 8. A method of locally administering a beneficial agent to a subject
5 which comprises implanting a system comprising a beneficial agent dissolved
6 or dispersed substantially throughout a viscous gel, the system releasing
7 within 24 hours after implantation not greater than 20% by weight of the
8 amount of beneficial agent to be delivered over the duration of the delivery
9 period.

10 9. The method of Claim 8 wherein the viscous gel comprises a
11 biocompatible polymer and a solvent.

12 10. The method of Claim 9 in which the viscous gel optionally includes
13 one or more of the following: an emulsifying agent, a pore former, a solubility
14 modulator for the beneficial agent, and an osmotic agent.

15 11. The method of Claim 10 wherein the solvent comprises a solvent
16 having a miscibility in water of less than 7% by weight.

17 12. The method of Claim 11 wherein the solvent is selected from
18 lower alkyl and aralkyl esters of aryl acids; aryl, aralkyl and lower alkyl
19 ketones; and lower alkyl esters of citric acid.

20 13. The method of Claim 9 wherein the polymer is selected from the
21 group consisting of polylactides, polyglycolides, polycaprolactones,
22 polyanhydrides, polyamines, polyurethanes, polyesteramides,
23 polyorthoesters, polydioxanones, polyacetals, polyketals, polycarbonates,
24 polyorthocarbonates, polyphosphazenes, succinates, poly(malic acid),

1 comprises a single solvent or a mixture of solvents with at least one solvent
2 having a miscibility in water of less than 7% by weight and the total amount of
3 solvent constituting 40% or more by weight of the gel vehicle, said
4 composition having a burst index of 8 or less.

5 19. An implantable, biodegradable composition for the sustained
6 delivery of a beneficial agent to a subject wherein the composition comprises
7 a polymer; an effective plasticizing amount of a solvent to form a viscous gel
8 with the polymer; and a beneficial agent dissolved or dispersed in the gel,
9 wherein the solvent comprises a mixture of solvents with at least one solvent
10 in the mixture having a miscibility in water of less than 7% by weight.

11 20. The composition of Claim 19 wherein the miscibility in water of the
12 solvent mixture is 10% or less by weight.

13 21. An implantable, biodegradable composition for delivery of a
14 beneficial agent to a subject wherein the composition comprises a polymer;
15 an effective plasticizing amount of a solvent to form a viscous gel with the
16 polymer; and a beneficial agent dissolved or dispersed in the gel, wherein the
17 solvent comprises a single solvent or a mixture of solvents with at least one
18 solvent having a miscibility in water of less than 7% by weight selected from
19 lower alkyl and aralkyl esters of benzoic acid.

20 22. An implantable gel composition for delivery of a beneficial agent to
21 a subject comprising:

22 A) a biocompatible polymer;

1 C) a beneficial agent selected from the group consisting of cDNA, DNA,
2 peptides, proteins and fragments and derivatives thereof, and optionally, one or more
3 of the following:

4 D) an emulsifying agent;

5 E) a pore former;

6 F) a solubility modulator for the beneficial agent; and

7 G) an osmotic agent.

8 wherein the composition has a burst index of less than 8.

9 28. A kit for administration of a beneficial agent to a subject comprising:

10 A) a biocompatible polymer;

11 B) a solvent having a miscibility in water of 7% or less by weight that is suitable
12 for dissolving the polymer and forming a viscous gel;

13 C) a beneficial agent; and optionally, one or more of the following:

14 D) an emulsifying agent;

15 E) a pore former;

16 F) a solubility modulator for the beneficial agent, optionally associated with the
17 beneficial agent; and

18 G) an osmotic agent;

19 wherein at least the beneficial agent, optionally associated with the solubility
20 modulator, is maintained separated from the solvent until the time of administration of
21 the beneficial agent to a subject.

22 29. An implantable composition for the systemic delivery of a beneficial agent
23 comprising a poly(lactide-co-glycolide) copolymer; an effective plasticizing amount of a

1 41. The composition of Claim 35 in which the emulsifying agent is selected from
2 the group consisting of alcohols, propylene glycol, ethylene glycol, glycerol, water and
3 solutions and mixtures thereof.

4 42. The composition of Claim 35 wherein the emulsifying agent is selected from
5 the group consisting of ethanol, isopropyl alcohol, water, solutions thereof, and
6 mixtures thereof.

7 43. The composition of Claim 30 wherein the copolymer has a monomer ratio of
8 lactic acid to glycolic acid in the range of 100:0 to about 15:85.

9 44. The composition of Claim 30 wherein the copolymer has a number average
10 molecular weight of from 1,000 to 120,000.

11 45. The composition of Claim 30 wherein the solvent comprises a component
12 solvent miscible with the solvent.

13 46. The composition of Claim 45 wherein the component solvent is selected
14 from the group consisting of triacetin, diacetin, tributyrin, triethyl citrate, tributyl citrate,
15 acetyl triethyl citrate, acetyl tributyl citrate, triethylglycerides, triethyl phosphate, diethyl
16 phthalate, diethyl tartrate, mineral oil, polybutene, silicone fluid, glylcerin, ethylene
17 glycol, polyethylene glycol, octanol, ethyl lactate, propylene glycol, propylene
18 carbonate, ethylene carbonate, butyrolactone, ethylene oxide, propylene oxide, N-
19 methyl-2-pyrrolidone, 2-pyrrolidone, glycerol formal, methyl acetate, ethyl acetate,
20 methyl ethyl ketone, dimethylformamide, dimethyl sulfoxide, tetrahydrofuran,
21 caprolactam, decylmethylsulfoxide, oleic acid, and 1-dodecylazacyclo-heptan-2-one,
22 and mixtures thereof.

1 59. The composition of Claim 18 wherein the gel remains non-rigid after
2 implantation.

3 60. The composition of Claim 59 wherein the gel maintains a glass transition
4 temperature below 37°C for at least 24 hours after implantation.

5 61. An implantable gel composition comprising a biocompatible polymer, a
6 biocompatible solvent forming a viscous gel with the polymer, and a beneficial agent,
7 the composition imbibing 40% or less of its bulk weight in water within the first 21 days
8 after implantation.

9 62. The composition of Claim 61 wherein the composition imbibes less than
10 30% of its bulk weight in water within the first 14 days after implantation.

11 63. The composition of Claim 62 wherein the composition imbibes less than
12 25% of its bulk weight in water within the first 7 days after implantation.

2 / 7

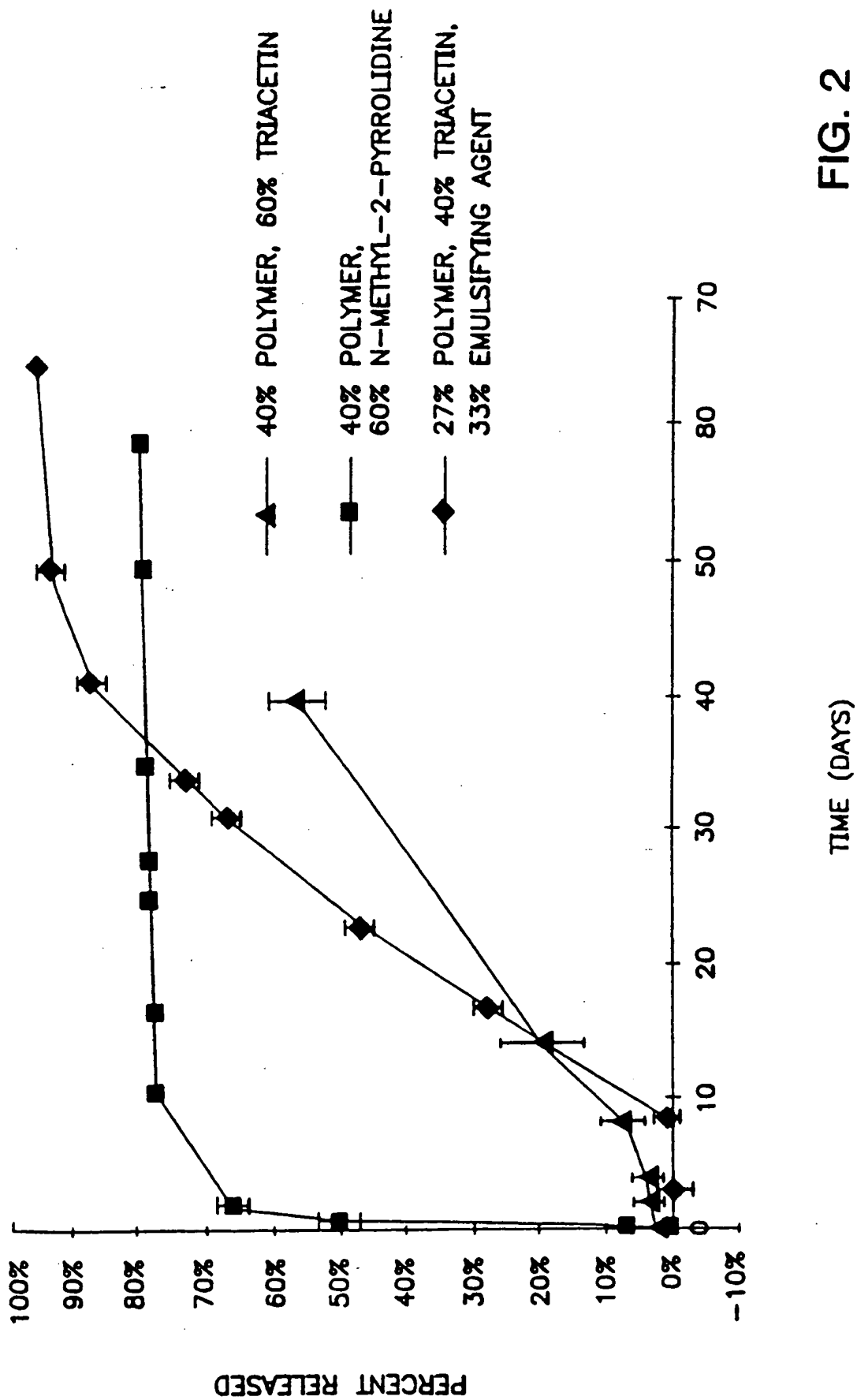


FIG. 2

4 / 7

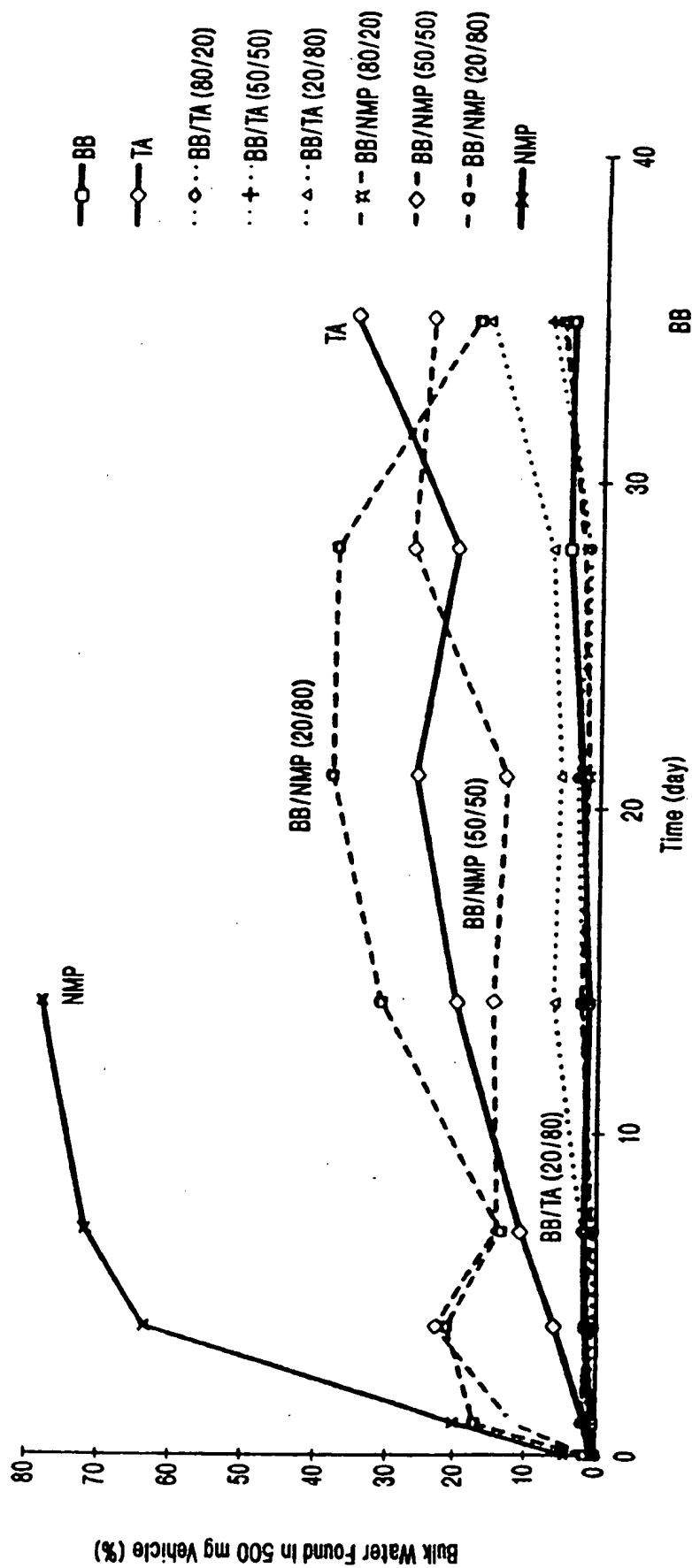


FIG. 4A

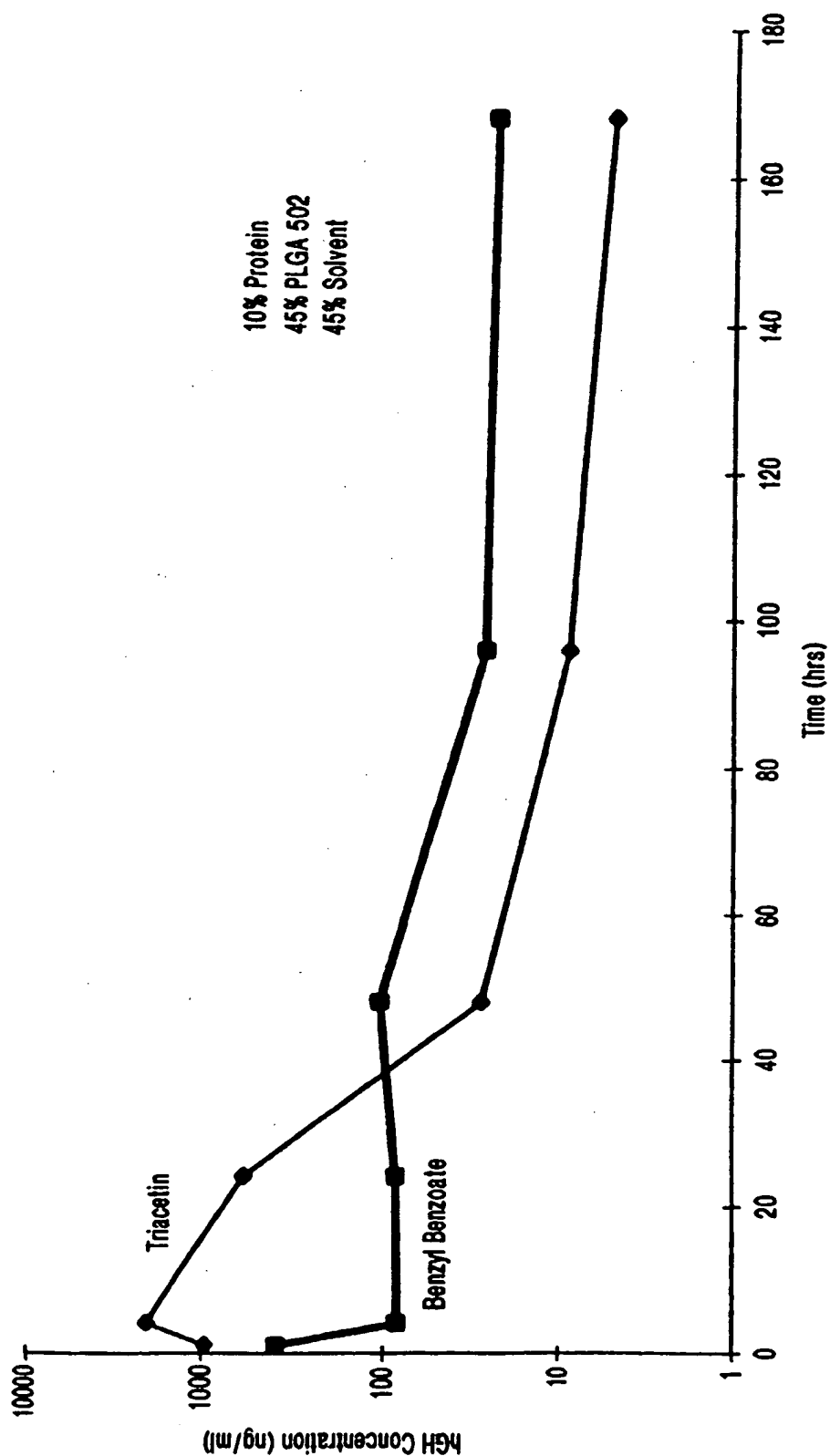


FIG. 5A